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Antifungal treatment strategies to reduce mortality in ıntensive care

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Abstract

Aim: Mortality of fungal infections is high in intensive care units. Waiting for culture results to start antifungal medication may lead to treatment delay and death. This study aimed to evaluate the mortality of adult patients who were administered antifungal medication for the treatment of culture-proven or possible invasive fungal infections in intensive care units.

Material and Methods: Data from patients who received antifungal therapy in a tertiary intensive care unit over a 24-month period were used. Fungal agents growing in the materials taken from the patients, APACHE II scores of the patients, antifungal drugs administered, and survival status were recorded. Results: 320 patients were included in the study. Antifungal medications were started prophylactically in 42.5%, empirically in 37.2%, and targetedly in 20.3%. Of the patients who received prophylactic treatment, 50.7% died, while 70.6% of empirical, and 66.2% of targeted therapy patients died. Applying prophylactic antifungal treatment significantly reduced the mortality rate compared to empirical and targeted treatments (p=0.003 and p=0.04, respectively). The most frequently occurring fungal agent in culture samples was Candida albicans (43.5%). The most commonly used antifungal drug was fluconazole (69.7%). The mean values of the Apache II score and colonization index were statistically significantly higher in deceased patients than in survivors (p=0.023 and p=0.027, respectively).

Discussion: In this study, it was shown that applying prophylactic antifungal treatment to patient groups at risk of invasive fungal infection before colonization develops reduces mortality. Our results support the use of prophylactic antifungal drugs to reduce mortality in intensive care units.

Keywords

Antifungal Drug, Intensive Care Unit, Prophylactic Use

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Introduction

Human fungal diseases are infections caused by any fungus that invades human tissues and can cause superficial, subcutaneous, or systemic disease. Infective fungi that enter human tissues and organs pose a significant threat to millions of individuals with weakened immune systems [1]. Fungal infections affect the lives of more than 6.5 million people worldwide each year, causing 3.5 million deaths [2]. Invasive fungal infections (IFI) include fungal infections in the bloodstream and/or deep tissues in a sterile area [3]. It has been reported that patients in the intensive care unit are at risk of IFI due to many reasons such as vascular catheters, broad-spectrum antimicrobial therapy, renal failure, total parenteral nutrition, and immunosuppressive agents [4]. Mortality rates in intensive care patients due to IFI can reach 30-40% [5], even 80% [6]. The role of antifungal therapy before culture diagnosis in the intensive care unit has not yet been fully defined, as there are uncertainties in identifying patients at high risk for developing IFI. The lack of well-established molecular techniques for early detection of candidemia frequently delays the recognition and treatment of this infection [7]. A delay in initiation of antifungal therapy has been reported to be associated with increased mortality [4]. Early antifungal strategies (prophylaxis, empiric, and preventive) have been developed using tools such as the Candida colonization index, clinical prediction rules, and non-culture-based fungal tests [8]. Cohort studies suggest that timely application of antifungal therapy and adequate source control are crucial [9].

This study aimed to contribute to the controversial issue of antifungal treatment strategies by examining the mortality rates of adult patients who received antifungal therapy for culture-proven or probable IFI in the tertiary intensive care units of one of the largest hospitals in the region with a high patient density in the south of Turkey.

Material and Methods

All adult patients who were hospitalized in the general intensive care and anesthesia resuscitation intensive care units of the Adana City Education and Research Hospital between January 2022 and December 2023 (2 years) and received antifungal treatment were included in the study. Patient files registered in the hospital information system with the researchers' personal passwords were examined. Patients' age, gender, indications for intensive care, additional diseases, Acute Physiology and Chronic Health Evaluation II (APACHE) II scores, colonization index, fungal agents grown in materials taken from patients, antifungal drugs used, indications for starting antifungal drugs, recovery, and death status were recorded. Antifungal treatments were started with the approval of an infectious diseases specialist physician. Patients were divided into 3 groups according to the status of starting antifungal treatment [10].

1. Prophylactic group: Antifungal drugs initiated for patients without IFI and at risk of IFI,
2. Empirical group: Antifungals initiated for patients with clinical signs and symptoms but no known source, suspected IFI, also considering the colonization index,
3. Targeted group: Antifungals initiated for patients with fungal growth detected as a result of cultures taken from sterile areas such as blood, pleura, peritoneum, and tissue constitute the targeted treatment group [10].

APACHE II score was calculated by recording age, fever, mean blood pressure, heart rate, respiratory rate, hematocrit, white blood cell, serum sodium, potassium, creatinine, pH value, acute renal failure, chronic disease, and postoperative status parameters electronically for each patient during the first 24 hours of admission to the intensive care unit. Blood and urine cultures were routinely obtained from all patients on their first admission to the intensive care unit. If necessary, aspirate, and sputum, among others, were added [11]. Cultures were repeated in cases such as fever and secretion increase according to the patient's clinical condition during the intensive care unit stay. The Colonization index (CI) was calculated by the ratio of the number of culture-positive areas to the number of cultured areas. Species-level identifications in the materials taken for culture were made in the microbiology laboratory using the BD BACTECTM FX (Becton Dickinson, USA) automated blood culture system, Sabouraud dextrose agar (RTA, TR), and MALDI-TOF MS (Bruker Daltonies, USA) yeast identification system.

Statistical Analysis

The Kolmogorov-Simirnov test was performed for normality analysis. Summary statistics were calculated for the patients' demographics, duration of stay in the intensive care unit, medical history, antifungal agents and therapy types, and microbiologic culture results. The difference between prophylactic, empiric, and therapeutic treatments on patient survival was analyzed using the Chi-square test. The Apache II scores of patients who were divided according to their survival outcome were analyzed with the Man-Whitney U test. The Apache II scores of patients who received prophylactic, empirical, and therapeutic treatments were analyzed using the Kruskal-Wallis test. Also, the colonization index of patients, grouped according to their survival outcome, was analyzed using the Mann-Whitney U test. Statistical analyses were performed by SPSS 27 software (SPSS Inc, Chicago, IL, USA). In addition, a p-value of less than 0.05 was considered statistically significant.

Ethical Approval

This study was approved by the Ethics Committee of Adana City Education and Research Hospital (Date: 2023-12-21, No:3027).

Results

During the 24 months, 320 of 2528 patients in intensive care receiving antifungal treatment were included in the study. 111 (34.7%) were women, and 209 (65.3%) were men. The average age of the patients is 64.5/year (18-98). The average length of stay in the intensive care unit was 35.16±26.9 days. Of the patients, 196 (61.3%) passed away, while 124 (38.7%) recovered and were transferred to the ward. The oxygen needs of the patients were provided by nasal cannula (n = 104), mask (n = 10), or mechanical ventilation (n = 206). Patients were admitted to intensive care for postoperative (n=129), lung-related diseases (n=75), general condition disorders due to underlying cancer (n=39), cardiovascular diseases (n=26), kidney-related diseases (n=30), cerebrovascular diseases (n=30), and other conditions (n=21). When examining the additional diseases of the patients, 193 (60.31%) had no comorbidities, 71 (22.19%) had one

Table 1. Antifungal therapy, antifungal drugs, mortality

		All patients n=320 (%value: n/320)	Prophylactic n=136 (%value: n/136)	Empiric n=119 (%value: n/119)	Therapeutic n=65 (%value: n/65)
Antifungal drugs	Fluconazole	n=223 (69.7%)	n=102 (75%)	n=95 (79.8%)	n=26 (40%)
	Amphotericin B	n=25 (7.8%)	n=14 (10.3%)	n=7 (5.9%)	n=4 (6.2%)
	Anidulafungin	n=33 (10.3%)	n=11 (8.1%)	n=9 (7.6%)	n=13 (20%)
	Micafungin	n=25 (7.8%)	n=4 (2.9%)	n=4 (3.4%)	n=17/26.1%
	Voriconazole	n=10 (3.1%)	n=5/136 (3.7%)	n=4 (3.4%)	n=1 (1.5%)
	Caspofungin	n=4 (1.3%)			n=4 (6.2%)
Mortality		n=196 (61.3%)	n=69 (%50.7)	n=84 (%70.6)	n=43 (%66.2)

n: number of patients

Table 2. Number and percentages of fungal species detected in culture

Numbers and percentages of fungal species	Blood culture (n=57)	Pleural culture (n=3)	Peritoneal fluid (n=2)	Tissue biopsy n=3	Urine culture (n=131)	Sputum culture (n=4)	Aspirate (n=34)
C. albicans n=100 (43.5%)	19	2	1		55	2	21
C. tropicalis n=63 (27.4%)	11				46		6
		-	-			-	
C. glabrata n=19 (8.3%)	9	1	1		6		2
						-	
C. parapsilozis n=15 (6.5%)	9				5		1
		-	-			-	
C. crusei n=10 (4.4%)	1				8		1
		-	-			-	
C.kefry n=9 (3.9%)	3	1			4		1
			-			-	
C.fabiani n=1 (0.4%)					1		
	-	-	-			-	-
C. lusitaniae n=2 (0,9%)					2		
	-	-	-			-	-
C. auris n=3 (1.3%)	3						
		-	-		-	-	-
C. metapsilosis n=2 (0.9%)	2						
		-	-		-	-	-
Trichosporon asaii n=2 (0.9%)					2		
	-	-	-			-	-
A. fumigatus n=3 (1.3%)						2	1
	-	-	-		-		
A. niger n=1 (0.4%)							1
	-	-	-		-	-	
Mucor mycozis				3			

n: number of patients C: candida A: aspergillus

comorbidity, and 56 (17.5%) had two or more comorbidities recorded. Mortality increased significantly in those with two or more comorbidities compared to those without comorbidities (p=0.004).

The indication for starting antifungal treatment was defined as prophylactic in 42.5% (n=136), empirical in 37.2% (n=119), and targeted in 20.3% (n=65) (Table 1). The most used antifungal drug is fluconazole, 69.7% (n = 223). In second place, amphotericin B was preferred in prophylaxis, anidulafungin was preferred in empirical treatment, and micafungin was preferred in targeted therapy (Table 1). The number and percentage values of patients using prophylactic, empirical, and targeted antifungals are shown in Table 1. 50.7% of the patients in whom prophylactic antifungal treatment was initiated, 70.6% in whom empirical antifungal therapy was initiated, and 66.2% in whom targeted antifungal therapy was initiated died (Table 1). It was observed that the mortality rates of patients who started prophylactic antifungal treatment were significantly lower than those who received empirical and targeted treatment (p = 0.003 and p = 0.04, respectively). There was no significant difference between the death rates of patients receiving empirical and targeted antifungal therapy (p = 0.534).

The APACHE II score was calculated at the patient's admission to the intensive care unit. APACHE II score mean values are close to each other in the prophylactic (31.7±11.7), empirical (32.7±10.6), and goal-directed (32±10.45) groups (p=0.989). The average Apache II score value of the deceased (33.79±10.1) was found to be significantly higher than that of the survivors

(29.79±11.94) (p=0.023).

Colonization index values were found to be significantly higher in the deceased (0.16±0.16) than in the survivors (0.12±0.17) (p=0.027).

In this study, no growth was detected in the culture samples taken from the patients in 136 cases, and prophylactic antifungal treatment was started. Empiric antifungal treatment was started in 119 cases. Growth was detected in blood, pleural peritoneal fluid, and tissue biopsy materials in 68 cases, and targeted antifungal treatment was started. The most frequently isolated fungal agent was found to be Candida albicans (43.5%). Other species that follow are Candida tropicalis, Candida glabrata, Candida parapsilosis, Candida crusei, and others. The fungal species growing in culture samples, the number of patients, and their percentages are shown in Table 2.

Discussion

Fungi are responsible for approximately 20% of microbiologically documented infections in intensive care units [12]. There is no consensus on systemic antifungal treatment strategies. Patients at risk of IFI are generally at risk of rapid clinical deterioration and death. Culture is the gold standard for confirming IFI, but waiting for culture results before starting antifungal medication may compromise patient outcomes [13]. In intensive care patients, it may be too late for antifungal treatment once colonization has developed. For this reason, intensive care patients are candidates for prophylactic antifungal administration at the beginning of hospitalization [14]. In antifungal treatment, the start time of treatment is as important as the choice of appropriate drug. It has been argued that fluconazole prophylaxis reduces both colonization and invasive candidemia in high-risk premature infants and can be administered safely without the development of fungal resistance [15]. In critically ill patients, prophylactic antifungals have been found to reduce IFI by half and mortality by a quarter, and antifungal prophylaxis with fluconazole has been recommended [16]. The necessity of antifungal prophylaxis during the treatment of some cancer patients is advocated. It has been shown that antifungal prophylaxis in high-risk neutropenic patients halves the number of patients receiving antifungals without increasing mortality or IFI [17]. It has been stated that antifungal prophylaxis is effective in high-risk patients, including high-risk liver transplant recipients [18] and critical surgical patients [19]. Almost all preventive studies have demonstrated or suggested a reduction in the administration and cost of antifungals with prophylactic antifungal use. However, the clinical validity of the strategy is still pending [20]. Our results also indicate that mortality decreases with prophylactic antifungal use. Since a delay in starting antifungal treatment in the intensive care unit can result in death, prophylactic use of antifungal drugs in patients at high risk of fungal infection can reduce delays in treatment.

Of course, since not all patients in the intensive care unit are at equal risk, routine prophylaxis cannot be recommended. In our study, the ratio of the number of patients receiving antifungal prophylaxis in two years to all intensive care patients is small (5.4%), but it is an important step in terms of reducing mortality. In this study, the low mortality rate in the patient group requiring prophylactic antifungal medication indicates that the patient group at risk of IFI was correctly identified. Candida, which has been considered for years primarily as an opportunistic pathogen of immunocompromised hosts (i.e., neutropenic cancer patients and organ transplant patients), has emerged as a significant cause of morbidity and mortality in surgical and intensive care unit patients in the last two decades [21]. According to this study's results and similar previous studies, it can be said that antifungal prophylaxis should not be limited only to neutropenic patients, but may also be beneficial for selected critically ill patients. The idea of expanding it to include the prevention of candida infections in a larger population of critically ill patients without neutropenia in the intensive care unit may be attractive.

Due to the high cost of antifungal treatment and the risk of toxicity development, it is not advisable to apply prophylaxis to every intensive care patient [14]. The effectiveness of azole prophylaxis in non-neutropenic high-risk intensive care patients is controversial. Some authors argue that increased application of azoles leads to a rise in resistant non-albicans Candida spp [10]. In order not to be late for treatment and not to cause excessive antifungal use, it is critical to accurately identify the patient group to which antifungal medication should be administered and the time of administration. Thus, treatment can be provided without increasing costs and side effects. It has been stated that the colonization index is one of several additional factors that can certainly be taken into account to increase the precision of patient selection and reduce the number of patients requiring antifungal therapy without increasing morbidity and mortality [21]. In our study, the colonization index was effective in the decision to start empirical antifungal treatment. The higher colonization index calculated in deceased patients confirms that this parameter should not be ignored. It has been shown that there is a decrease in colonization with prophylaxis in the risk group [22]. This study demonstrated that applying prophylactic antifungal treatment to patient groups at risk of IFI before colonization develops reduces mortality. It has been stated that azole-derived antifungals are safe due to their low cost and low toxicity [18]. Similar to previous research results [10], in our study, 400mg fluconazole was the most preferred antifungal for prophylaxis when used intravenously.

It is known that C. albicans is the most common species in Europe [5], and candidemia is the most common serious fungal infection developing in critically ill patients in intensive care units [23]. It has been stated that Candida spp. is the third leading cause of infections in the intensive care unit and accounts for 90% of fungal infections [6,24]. In our study, the most common fungal genus detected in intensive care patients was candida.

Previous studies have determined that APACHE II scores are independently associated with hospital mortality [25]. Similarly, in this study, mortality was found to be higher in patients with high APACHE II scores. Since the main purpose of this study was to compare mortality in prophylactic empirical target groups, the lack of difference between the APACHE II scores of these three groups demonstrated that mortality decreased with prophylactic antifungal use. Although the patients' oxygen

needs, indications for intensive care admission, and comorbid diseases were heterogeneous, the similarity of APACHE II scores among the three groups allowed us to better evaluate mortality rates. Although there was no difference in the expected mortality rates in the three groups in this study, it can be said that prophylactic antifungal use increases survival based on the result that mortality was low in the prophylactic group.

Conclusion

In this study, it was found that prophylactic antifungal administration to patients considered to be at high risk of developing IFI reduced mortality.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or compareable ethical standards.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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